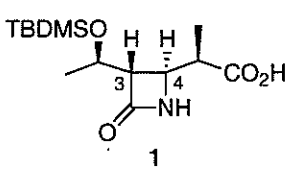
DOUBLE STEREODIFFERENTIATION IN INTRAMOLECULAR C-H INSERTION REACTION TOWARD THE SYNTHESIS OF 1β-METHYLCARBAPENEM ANTIBIOTICS†

Masahiro Anada, Shinji Kitagaki, and Shunichi Hashimoto*

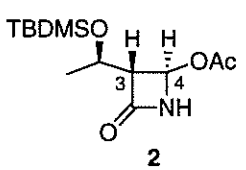
Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

Abstract – A double asymmetric induction in intramolecular C-H insertion reaction of chiral, non-racemic α-diazo amides has been explored with the aid of dirhodium(II) tetrakis[*N*-phthaloyl-(*R*)- or (*S*)-phenylalaninate], Rh_2(*R*- or *S*-PTPA)$_4$, as a homochiral catalyst. The combination of α-methoxycarbonyl-α-diazoacetamide (**13**) with Rh_2(*S*-PTPA)$_4$ provides an 85:15 mixture of the desired 3-oxa-1-azabicyclo[4.2.0]octane derivative (**14**) and its diastereomer (**15**), which, upon reduction with $LiBH_4$ and subsequent ready separation, leads to a key intermediate for the synthesis of 1β-methylcarbapenem antibiotics. Doyle-Taber's C-H insertion model coupled with the solid state structure of Rh_2(*S*-PTPA)$_4$ confirms the observed diastereomer preference.

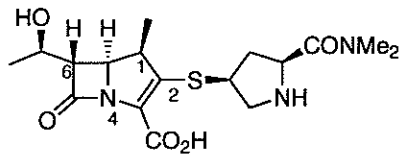
Since the discovery that installation of a β-methyl substituent at C-1 of the carbapenem skeleton enhances chemical and metabolic stability, an enormous amount of effort has been devoted to the stereocontrolled synthesis of (3*S*,4*S*)-3-[(*R*)-1'-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(*R*)-1-carboxyethyl]azetidin-2-one (**1**) possessing the required four contiguous stereogenic centers, a pivotal precursor to 1β-methylcarbapenem antibiotics (*e.g.*, meropenem).[1,2] Most of the reported syntheses of **1** have commenced with commercially available (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1'-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (**2**), wherein many innovative tactics for a stereocontrolled introduction of the β-methyl group have been devised. While the most popular and successful methods have relied on aldol-type condensation of **2** with properly designed chiral and achiral metal enolates of propionic acid derivatives,[3,4] there have been developed several alternatives involving reduction of olefinic precursors



1

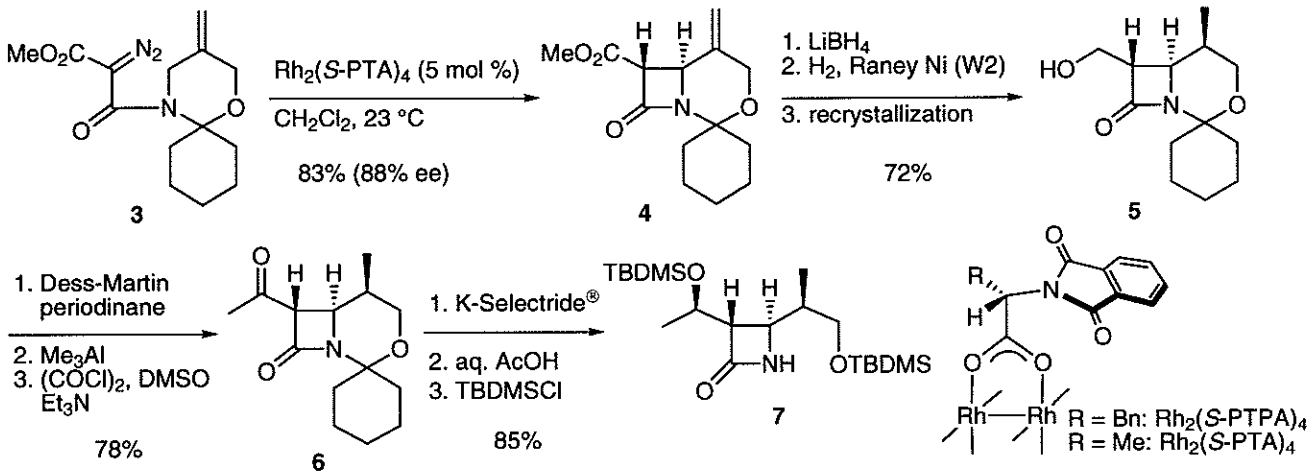


2



Meropenem®

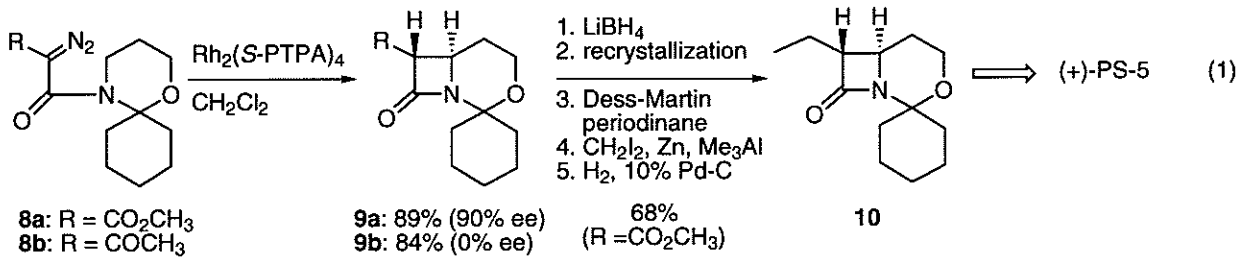
†Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.



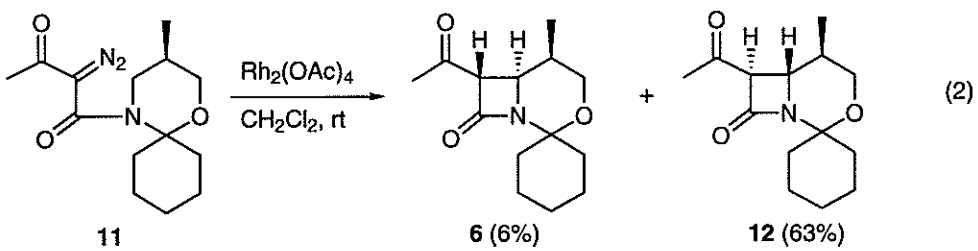
Scheme 1

of **1**,[5-7] reduction of a hexacarbonyldicobalt-stabilized propargyl cation,[8] decarboxylation of malonic acid derivatives,[9] and asymmetric hydroformylation of 4-vinylazetidin-2-one derivative.[10]

Independently of these strategies, we recently reported a highly enantioselective construction of 3-oxa-1-azabicyclo[4.2.0]octane derivative (**4**) by intramolecular C-H insertion of α-methoxycarbonyl-α-diazoacetamide (**3**) catalyzed by dirhodium(II) complexes incorporating *N*-phthaloyl-(*S*)-amino acids, which leads to the key azetidin-2-one (**7**) for the synthesis of 1β-methylcarbapenems (Scheme 1).[11] For a closely related cyclization, it was also demonstrated that switching the α-substituent of the diazo carbon from a methoxycarbonyl group to a synthetically more advantageous acetyl group provided no asymmetric induction [eqn. (1)]. In this context, of particular interest was an alternative approach developed by Brown and Southgate.[12] They previously reported that $Rh_2(OAc)_4$-catalyzed C-H

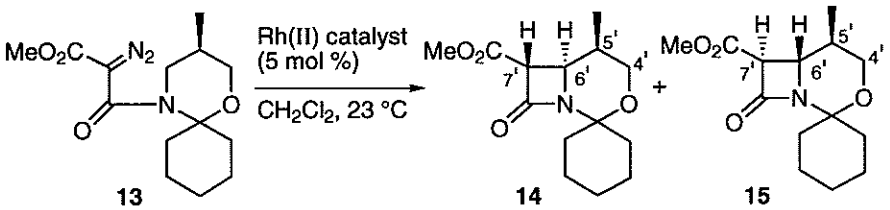


insertion reaction of an optically active α-diazoacetoacetamide (**11**) bearing a methyl group at C-5 of the tetrahydro-1,3-oxazine ring system proceeded with high diastereoselectivity, but the preferred cyclization product was the undesired diastereomer (**12**) [eqn. (2)]. As a solution to this problem, we were now intrigued by the feasibility of a double asymmetric induction by means of homochiral dirhodium(II) carboxylates.[13,14]



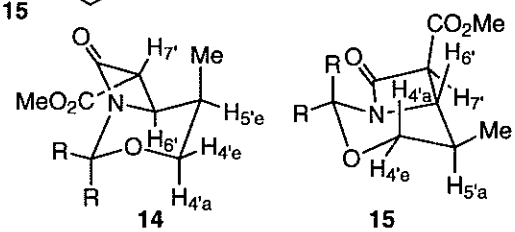
Armed with our findings, we explored cyclization of an optically active α-methoxycarbonyl-α-diazoacetamide (**13**) using dirhodium(II) tetrakis[*N*-phthaloyl-(*R*)- and (*S*)-phenylalaninate], Rh_2(*R*-PTPA)$_4$ and Rh_2(*S*-PTPA)$_4$, as homochiral catalysts and $Rh_2(OAc)_4$ as an achiral catalyst.[15] A set of experiments were carried out in CH_2Cl_2 in the presence of 5 mol % of catalyst at 23 °C. The sense and degree of diastereoselection were determined by ^{1}H NMR analysis of the crude product. The desired product (**14**) showed two small coupling constants of 2.4 Hz ($J_{4'a,5'e}$) and 2.7 Hz ($J_{4'e,5'e}$), whereas the undesired diastereomer (**15**) displayed a large axial-axial coupling constant of 11.2 Hz ($J_{4'a,5'a}$) and a small axial-equatorial one of 4.6 Hz ($J_{4'e,5'a}$).[16] In the present reactions, no trace of 6',7'-*cis* isomers could be detected. The results are presented in Table 1. As expected from the precedent set by Brown

Table 1. Diastereoselective C-H Insertion Reaction of α-Methoxycarbonyl-α-diazoacetamide (**13**)



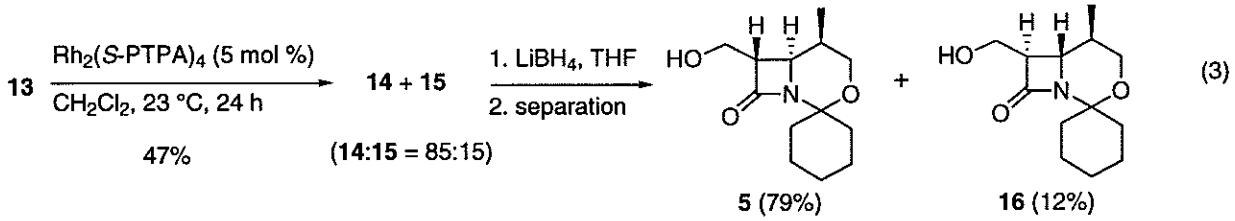
entry	Rh(II) catalyst	time, h	% yield[a]	**14**:**15**[b]
1	$Rh_2(OAc)_4$	18	75	25:75
2	Rh_2(*R*-PTPA)$_4$	18	77	2:98
3	Rh_2(*S*-PTPA)$_4$	24	47	85:15

[a] Combined yield of **14** and **15**. [b]Determined by ^{1}H NMR analysis of the crude product.



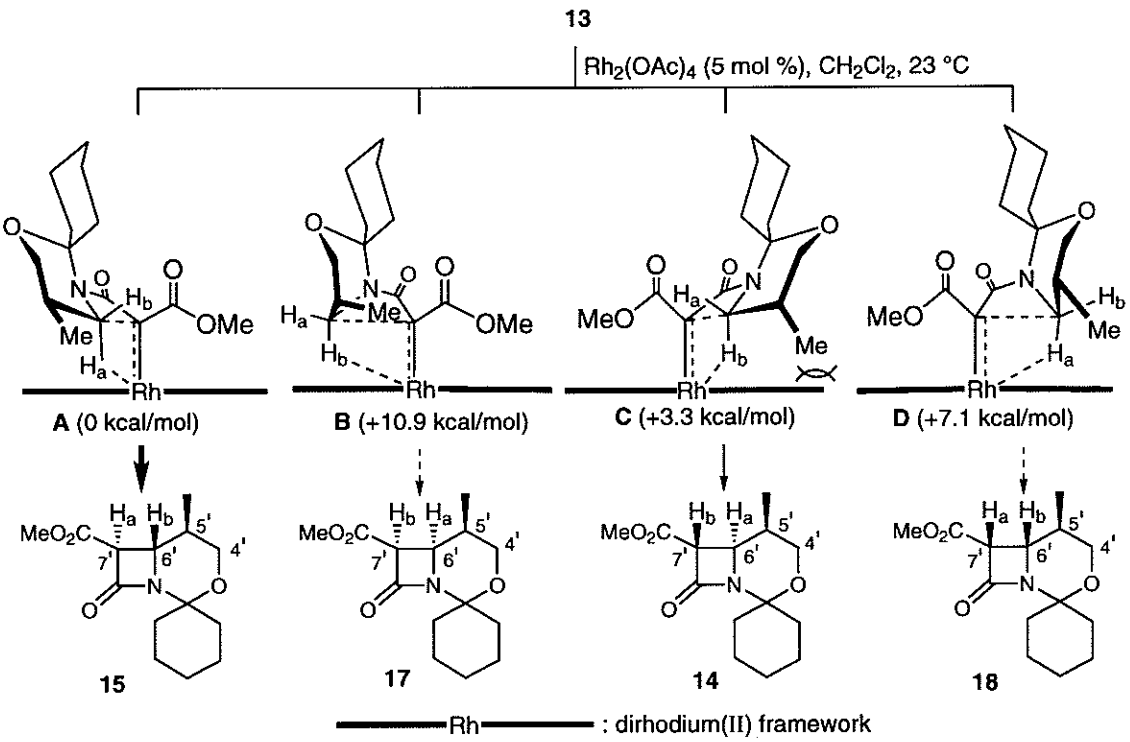
and Southgate,[12] the catalysis of **13** using $Rh_2(OAc)_4$ provided the undesired diastereomer (**15**) as the major product, wherein the ratio of 25:75 was much smaller than that observed with **11**. This result, together with our previous findings described above, suggested that combinations of **13** / Rh_2(*R*-PTPA)$_4$ and **13** / Rh_2(*S*-PTPA)$_4$ should constitute matched and mismatched pairs, respectively. Indeed, the choice of Rh_2(*R*-PTPA)$_4$ afforded a mixture of **14** and **15** in an exceptionally high ratio of 2:98. To our delight, even a mismatched pair using Rh_2(*S*-PTPA)$_4$ was found to bring about a reversal in the inherent diastereoselection in this system to result in a ratio of 85:15 favoring the desired product (**14**), *albeit* in modest yield. It is worthy of note that the chirality of the dirhodium(II) catalysts rather than that of the substrate (**13**) dictates the stereochemical course of this process.

Separation of **14** from **15** was difficult so that the mixture (**14**:**15**=85:15) was directly reduced with $LiBH_4$ to give readily separable alcohols (**5**) and (**16**) [eqn. (3)]. The alcohol (**5**), mp 159-160 °C, $[\alpha]_D^{21}$



+17.0° (c=0.79, $CHCl_3$) {lit.,[11] mp 159-160 °C, $[\alpha]_D^{25}$ +16.9° (c=1.06, $CHCl_3$)}, exhibited identical spectroscopic data with those of a sample obtained in the previous work,[11] which confirmed the correctness of the foregoing stereochemical assignment.

The stereochemical outcome of C-H insertion reaction of **13** with the aid of $Rh_2(OAc)_4$ can be explained by the Doyle-Taber's mechanistic hypothesis, wherein it is requisite that the rhodium(II)-carbene bond is aligned with the target C-H bond in a transition state.[17,18] Assuming that planarity of the amide bond could be maintained during the C-H insertion reaction,[19,20] four competing transition states (**A**)-(**D**) can be presented (Scheme 2). Plausible cyclizations *via* the transition states (**B**) and (**D**), which lead to 6',7'-*cis* isomers, can be ruled out due to their high energy boat-like conformation. The high preference for the transition state (**A**) over the transition state (**C**) is understandable by considering the steric repulsion between the axial methyl group on the tetrahydro-1,3-oxazine ring and the dirhodium(II) framework in **C**, leading to the predominant formation of **15** in accord with the observed diastereoselection. It is noteworthy that the computational method developed by Taber estimates the transition state (**A**) to be favored by 3.3 kcal/mol compared to the transition state (**C**).[18,20]



Scheme 2

We may also explain the stereochemical course of double asymmetric C-H insertion reaction catalyzed by Rh_2(*S*-PTPA)$_4$, provided that the solid state structure of Rh_2(*S*-PTPA)$_4$, established as the bis(4-*tert*-butylpyridine)adduct by a single-crystal X-Ray structural analysis,[21] is available in solution (Figure 1). The notable feature of this structure is that two phthalimido groups in a pair of adjoining ligands are oriented to an axial coordination site of each octahedral rhodium. Looking down into the Rh-Rh axis, the chiral environment around the rhodium(II) center can be divided into four quadrants, of which two (the second and third quadrants) are occupied by the protruding phthalimido groups.[22] In other words,

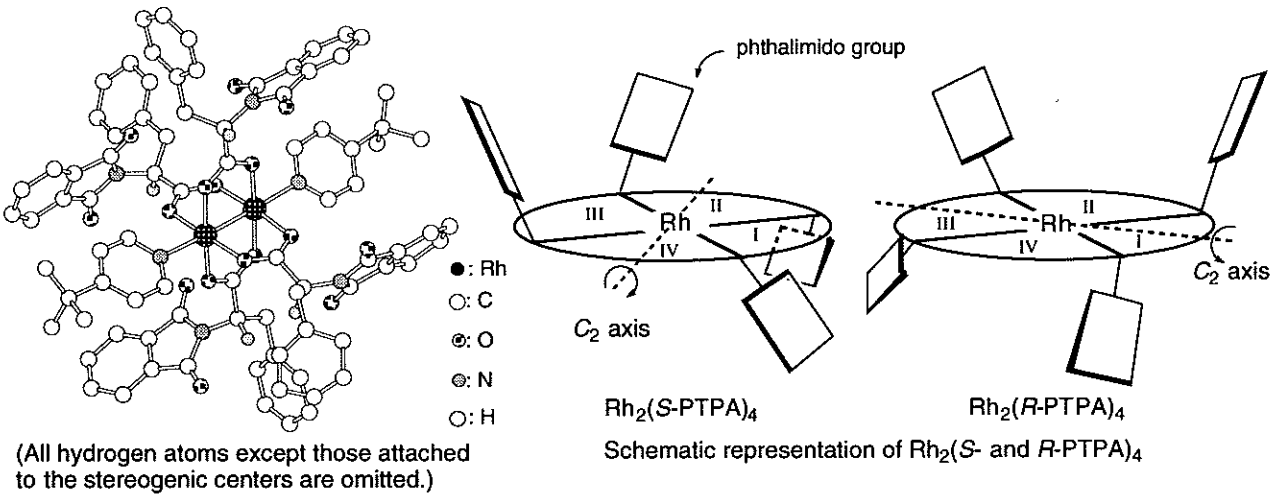
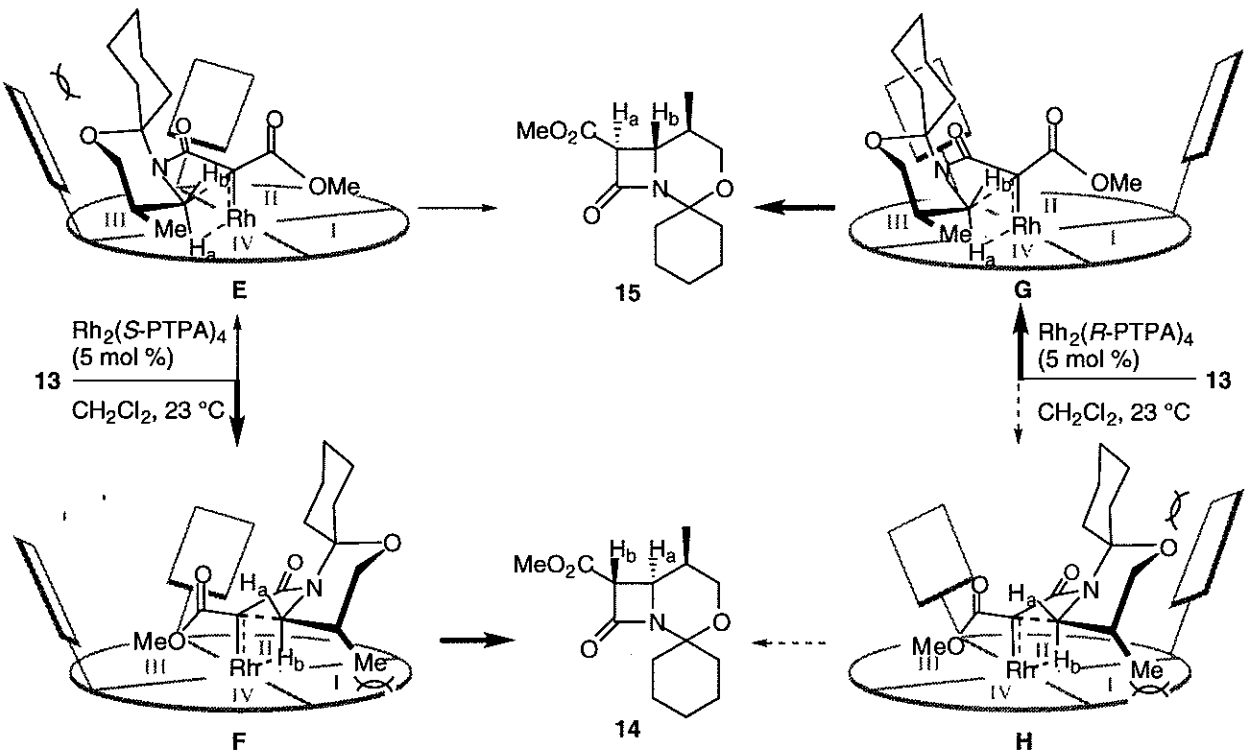


Figure 1. Crystal structure of bis(4-*tert*-butylpyridine) adduct of Rh_2(*S*-PTPA)$_4$

this structure model has C_2 symmetry-like conformation with the phthalimido groups aligned in a "down-down-up-up" arrangement. Taking account of the foregoing transition states (**A**) and (**C**), two transition states (**E**) and (**F**) can be presented where the ester group and the tetrahydro-1,3-oxazine ring system undergoing C-H insertion are accommodated in less crowded first and fourth quadrants (Scheme 3). Since the steric repulsion between the methyl group and the dirhodium(II) framework in **F** is less severe than that between the *N*,*O*-acetal moiety and the phthalimido group in **E**, the former is favored over the latter, providing the desired diastereomer (**14**) as the major product. A similar argument can be well applied to the case with Rh_2(*R*-PTPA)$_4$, wherein two transition states (**G**) and (**H**) can be presented. Clearly, the transition state (**G**) without considerable steric repulsion is preferred over the transition state (**H**), thereby leading to the virtually exclusive formation of **15** as observed.



Scheme 3

In summary, we have demonstrated that the chirality of Rh_2(*S*-PTPA)$_4$ can bring about a reversal in the inherent diastereoselection in C–H insertion reaction of an optically active α-methoxycarbonyl-α-diazoacetamide (**13**). The significance of this process has been verified by the formal synthesis of a key intermediate for the synthesis of 1β-methylcarbapenems. It is also worth noting that Doyle-Taber's C-H insertion model coupled with the solid state structure of Rh_2(*S*-PTPA)$_4$ predicts the observed diastereomer preference.

EXPERIMENTAL

General. Melting points were determined on a Büchi 535 digital melting apparatus and are uncorrected. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. IR spectra were recorded on a Jasco FT/IR-5300 spectrophotometer. NMR spectra were measured with JEOL JNM-AL 400 (^{1}H at 400 MHz and ^{13}C at 100 MHz) spectrometer, with tetramethylsilane (δ 0.0, ^{1}H) or chloroform-d_1 (δ 77.0, ^{13}C) as an internal standard. Electron impact MS spectra (EIMS) were obtained on a JEOL JMS-DX 303 spectrometer, operating with an ionization energy of 70 eV. Fast atom bombardment MS spectra (FABMS) were obtained on a JEOL JMS-HX 110 spectrometer. Column chromatography was performed on Merck silica gel 60, 70-230 mesh. Computational analysis was carried out according to the published method.[18,20] *p*-Acetamidobenzenesulfonyl azide[23] and (*R*)-3-amino-2-methyl-1-propanol[24] were prepared according to literature procedures.

Methyl (*R*)-2-Diazo-3-[3-methyl-1-oxa-5-azaspiro[5.5]undecan-5-yl]-3-oxopropanoate (13). A mixture of (*R*)-3-amino-2-methyl-1-propanol (1.07 g, 12.0 mmol) and cyclohexanone (1.20 g, 12.0 mmol) in toluene (50 mL) was refluxed for 6 h under azeotropic removal of water. The solution was cooled to rt, and *N*,*N*-dimethylaniline (1.82 g, 15.0 mmol) was added to the solution. A solution of methyl chloroformylacetate (1.80 g, 13.2 mmol) in toluene (10 mL) was added to the mixture at 0 °C. After 1.5 h of stirring at this temperature, the reaction was quenched by addition of Et_3N (1.52 g, 15.0 mmol), and the whole was partitioned between AcOEt (100 mL) and water (50 mL). The separated organic layer was washed successively with saturated $NaHCO_3$ solution (3 x 20 mL), water (2 x 20 mL), and brine (2 x 20 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* furnished the crude product (4.5 g of orange oil), which was purified by column chromatography on silica gel (50 g) with hexane-AcOEt (4:1) to give methyl (*R*)-3-[3-methyl-1-oxa-5-azaspiro[5.5]undecan-5-yl]-3-oxopropanoate (2.12 g, 71%) as colorless needles; mp 60.2-61.3 °C (^{i}Pr$_2$O-hexane); $[\alpha]_D^{25}$ +24.7° (c=1.00, $CHCl_3$); IR νmax (Nujol): 1740, 1640, 1200, 912, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.96 (d, *J* = 6.6 Hz, 3H, C3-C*H*$_3$), 1.15-1.81 (m, 8H, cyclohexane), 2.08-2.27 (m, 1H, C3-*H*), 2.57-2.68 (m, 2H, cyclohexane), 3.11 (dd, *J* = 9.2, 12.5 Hz, 1H, C2-*H*), 3.25 (dd, *J* = 7.3, 11.9 Hz, 1H, C4-*H*), 3.33 (dd, *J* = 5.3, 12.5 Hz, 1H, C2-*H*), 3.40 (d, *J* = 15.8 Hz, 1H, CH*H*CO$_2$Me), 3.44 (d, *J* = 15.8 Hz, 1H, C*H*HCO$_2$Me), 3.74 (s, 3H, CO$_2$C*H*$_3$), 3.93 (dd, *J* =8.6, 11.9 Hz, 1H, C4-*H*); ^{13}C NMR ($CDCl_3$) δ: 17.4, 22.5, 22.8, 24.8, 29.6, 30.2, 30.7, 43.8, 46.7, 52.3. 63.8, 90.6, 164.3, 168.2; EIMS *m/z* (rel. int. %): 269 (M$^+$, 19), 238 (6.4), 226 (40), 196 (53), 126 (100); HRMS (EI) *m/z*: Calcd for $C_{14}H_{23}NO_4$, 269.1627. Found 269.1609; Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61 N, 5.20. Found: C, 62.27; H, 8.58; N, 5.05.

A solution of *p*-acetamidobenzenesulfonyl azide (1.80 g, 7.5 mmol) in MeCN (5 mL) was added dropwise to a solution of methyl (*R*)-3-[3-methyl-1-oxa-5-azaspiro[5.5]undecan-5-yl]-3-oxopropanoate (2.00 g, 7.43 mmol) and DBU (1.22 g, 8.00 mmol) in MeCN (10 mL) at 0 °C. After 3 h of stirring at this temperature, the reaction mixture was partitioned between AcOEt (50 mL) and water (20 mL). The organic layer was washed successively with 10% NaOH solution (2 x 15 mL), water (2 x 15 mL), saturated NH_4Cl solution (20 mL), and brine (2 x 15 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* gave the crude product (4.1 g of yellow oil), which was purified by column chromatography on silica gel (30 g) with hexane-AcOEt (5:1) to provide **13** (2.06 g, 94%) as a yellow oil; $[\alpha]_D^{23}$ +9.15° (c=1.03, $CHCl_3$); IR νmax (film): 2128, 1719, 1628, 1399, 1296 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.90 (d, *J* = 6.8 Hz, 3H, C3-C*H*$_3$), 1.21-1.33 (m, 1H, cyclohexane), 1.41-1.61 (m, 5H, cyclohexane), 1.80-1.88 (m, 2H, cyclohexane), 2.14-2.27 (m, 1H, C3-*H*), 2.65 (dt, *J* = 4.0, 13.0 Hz, 1H, cyclohexane), 2.68 (dt, *J* = 4.0, 13.0 Hz, 1H, cyclohexane), 3.13 (dd, *J* = 11.2, 12.7 Hz, 1H, C2-*H*), 3.27-3.35 (m, 2H, C2-*H* and C4-*H*), 3.78 (s, 3H, CO_2CH_3), 3.89 (dd, *J* = 7.1, 11.2 Hz, 1H, C4-*H*); ^{13}C NMR ($CDCl_3$) δ: 16.6, 22.4, 22.9, 25.0, 29.9, 30.9, 31.0, 49.5, 52.1. 64.7, 67.9, 90.4, 160.6, 162.5; FABMS *m/z*: 296 (MH^+); HRMS (FAB) *m/z*: Calcd for $C_{14}H_{22}N_3O_4$, 296.1610. Found 296.1614; Anal. Calcd for $C_{14}H_{21}N_3O_4$: C, 56.94; H, 7.17; N, 14.23. Found: C, 57.18; H, 7.29; N, 14.15.

Intramolecular C-H Insertion Reaction of 13 (Table 1, entry 3). Bis(ethyl acetate) adduct of Rh_2(*S*-PTPA)$_4$[21,25] (330 mg, 0.21 mmol) was added to a solution of **13** (1.25 g, 4.24 mmol) in CH_2Cl_2 (15 mL) at 23 °C. After 24 h of stirring at this temperature, the reaction mixture was evaporated *in vacuo* and the residue (1.67 g of purple oil) was purified by column chromatography on silica gel (40 g) with hexane-AcOEt (3:1) to give the inseparable mixture of methyl (5'*R*,6'*R*,7'*R*)-5'-methyl-8'-oxospiro[cyclohexane-1,2'-[3]oxa[1]azabicyclo[4.2.0]octane]-7'-carboxylate (**14**) and methyl (5'*R*,6'*S*,7'*S*)-5'-methyl-8'-oxospiro[cyclohexane-1,2'-[3]oxa[1]azabicyclo[4.2.0]octane]-7'-carboxylate (**15**) (532 mg, 47%, **14**:**15** = 85:15) as a colorless oil; IR νmax (film): 1767, 1740, 1454 cm^{-1}; EIMS *m/z* (rel. int. %): 267 (M^+, 27), 224 (81), 124 (100); HRMS *m/z*: Calcd for $C_{14}H_{21}NO_4$, 267.1471. Found 267.1482.

14: ^1H NMR ($CDCl_3$) δ: 1.13 (d, *J* = 7.2 Hz, 3H, C5'-C*H*$_3$), 1.22-1.58 (m, 6H, cyclohexane), 1.61-1.90 (m, 4H, cyclohexane and C5'-*H*), 2.26-2.31 (m, 1H, cyclohexane), 3.59 (dd, *J* = 2.4, 12.0 Hz, 1H, C4'-*H*), 3.77 (s, 3H, CO_2CH_3), 3.85 (d, *J* = 2.0 Hz, 1H, C7'-*H*), 3.98 (dd, *J* = 2.7, 12.0 Hz, 1H, C4'-*H*), 4.04 (dd, *J* = 2.0, 4.9 Hz, 1H, C6'-*H*); ^{13}C NMR ($CDCl_3$) δ: 11.6, 21.8, 22.0, 25.1, 29.2, 30.8, 34.8, 49.9, 52.7, 56.6, 64.1, 85.3, 158.4, 167.7.

15: ^1H NMR ($CDCl_3$) δ: 0.90 (d, *J* = 6.8 Hz, 3H, C5'-C*H*$_3$), 1.20-1.31 (m, 1H, cyclohexane), 1.36-1.53 (m, 4H, cyclohexane), 1.61-1.90 (m, 5H, cyclohexane and C5'-*H*), 2.21-2.30 (m, 1H, cyclohexane), 3.42 (dd, *J* = 1.7, 9.6 Hz, 1H, C6'-*H*), 3.50 (dd, *J* = 11.2, 12.5 Hz, 1H, C4'-*H*), 3.62 (d, *J* = 1.7 Hz, 1H, C7'-*H*), 3.68 (dd, *J* = 4.6, 12.5 Hz, 1H, C4'-*H*), 3.77 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 12.7, 21.9, 22.1, 25.1, 30.3, 34.9, 35.3, 52.6, 52.8, 60.9. 64.1, 85.2, 158.4, 167.4.

(5'*R*,6'*R*,7'*S*)-7'-Hydroxymethyl-5'-methylspiro[cyclohexane-1,2'-[3]oxa[1]azabicyclo[4.2.0]octan]-8-one (5) and (5'*R*,6'*S*,7'*R*)-7'-Hydroxymethyl-5'-methylspiro[cyclohexane-1,2'-[3]oxa[1]azabicyclo-[4.2.0]octan]-8-one (16). A solution of the mixture of **14** and **15** (Table 1, entry 3, **14**:**15** = 85:15, 490 mg, 1.95 mmol) in THF (2 mL) was added dropwise to a solution of $LiBH_4$ (50 mg, 2.38 mmol) in THF

(2 mL) at 0 °C. After 3 h of stirring at this temperature, the reaction was quenched with water (2 mL). The whole mixture was poured into a two layer mixture of Et_2O (20 mL) and water (10 mL), and the layers were separated. The aqueous layer was extracted with AcOEt (2 x 15 mL), and the combined organic layers were washed with brine (2 x 5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (520 mg of colorless oil), which was purified by column chromatography on silica gel (40 g) with AcOEt to afford **5** (368 mg, 79%) as colorless plates and **16** (51.5 mg, 11%) as a colorless oil.

5: mp 159-160 °C (AcOEt-hexane) (lit.,[11] mp 159-160 °C); $[\alpha]_D^{21}$ +17.0° (c=0.79, $CHCl_3$) {lit.,[11] $[\alpha]_D^{25}$ +16.9° (c=1.06, $CHCl_3$)}; IR νmax (Nujol): 3436, 1732, 1372, 1042 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.11 (d, *J* = 7.3 Hz, 3H, C5'-C*H*$_3$), 1.31-1.52 (m, 4H, cyclohexane), 1.55-1.08 (m, 6H, cyclohexane and C5'-*H*), 2.22-2.38 (m, 1H, cyclohexane), 3.19 (ddd, *J* = 1.7, 6.5, 10.0 Hz, 1H, C7'-*H*), 3.47 (br s, 1H, O*H*), 3.58 (dd, *J* = 2.7, 12.2 Hz, 1H, C4'-*H*), 3.71 (dd, *J* = 1.7, 5.0 Hz, 1H, C6'-*H*), 3.82-4.00 (m, 3H, C*H*$_2$OH and C4'-*H*); ^{13}C NMR ($CDCl_3$) δ: 11.7, 21.8, 22.1, 25.2, 29.6, 31.1, 34.8, 50.0, 54.6, 59.7, 64.4, 85.0, 164.7; EIMS *m/z* (rel. int. %): 239 (M^+, 30), 196 (100); HRMS *m/z*: Calcd for $C_{13}H_{21}NO_3$, 239.1522. Found 239.1534; Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.84; N, 5.85. Found: C, 64.93; H, 8.77; N, 5.84.

16: $[\alpha]_D^{23}$ +20.7° (c=1.99, $CHCl_3$); IR νmax (film): 3436, 2936, 1732, 1372, 1042 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.87 (d, *J* = 6.6 Hz, 3H, C5'-C*H*$_3$), 1.32-1.57 (m, 4H, cyclohexane), 1.59-1.80 (m, 6H, cyclohexane and C5'-*H*), 2.23-2.80 (m, 1H, cyclohexane), 2.80 (br s, 1H, O*H*), 2.93 (ddd, *J* = 1.6, 6.0, 6.0 Hz, 1H, C7'-*H*), 3.08 (dd, *J* = 1.6, 10.0 Hz, 1H, C6'-*H*), 3.45 (dd, *J* = 11.2, 12.0 Hz, 1H, C4'-*H*), 3.65 (dd, *J* = 4.4, 12.0 Hz, 1H, C4'-*H*), 3.83-3.95 (m, 2H, C*H*$_2$OH); ^{13}C NMR ($CDCl_3$) δ: 12.9, 22.0, 22.2, 25.2, 30.4, 35.0, 35.5, 53.1, 59.6, 59.8, 64.4, 84.7, 164.8; EIMS *m/z* (rel. int. %): 239 (M^+, 27), 196 (100); HRMS *m/z*: Calcd for $C_{13}H_{21}NO_3$, 239.1522. Found 239.1539; Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.84; N, 5.85. Found: C, 65.03; H, 8.82; N, 5.83.

ACKNOWLEDGEMENT

This research was supported in part by the Special Coordination Funds of the Science and Technology Agency of the Japanese Government. The authors thank the Japan Society for the Promotion of Science for Research Fellowships for Young Scientists (to M. A.).

REFERENCES AND NOTES

1. D. H. Shih, F. Baker, L. Cama, and B. G. Christensen, *Heterocycles*, 1984, **21**, 29.
2. For reviews on syntheses of 1β-methylcarbapenem antibiotics, see: (a) Y. Ito and S. Terashima, *J. Synth. Org. Chem. Jpn.*, 1989, **47**, 606; (b) A. H. Berks, *Tetrahedron*, 1996, **52**, 331; (c) M. Sunagawa and A. Sasaki, *J. Synth. Org. Chem. Jpn.*, 1996, **54**, 761.
3. (a) Y. Nagao, T. Kumagai, S. Tamai, T. Abe, Y. Kuramoto, T. Taga, S. Aoyagi, Y. Nagase, M. Ochiai, Y. Inoue, and E. Fujita, *J. Am. Chem. Soc.*, 1986, **108**, 4673; (b) L. M. Fuentes, I. Shinkai, and T. N. Salzmann, *J. Am. Chem. Soc.*, 1986, **108**, 4675.
4. (a) R. Déziel and D. Favreau, *Tetrahedron Lett.*, 1986, **27**, 5687; (b) F. Shirai and T. Nakai, *J. Org. Chem.*, 1987, **52**, 5491; (c) A. Martel, J.-P. Daris, C. Bachand, J. Corbeil, and M. Menard, *Can. J. Chem.*, 1988, **66**, 1537; (d) T. Shibata and Y. Sugimura, *J. Antibiot.*, 1989, **42**, 374; (e) Y. Ito, A.

Sasaki, K. Tamoto, M. Sunagawa, and S. Terashima, *Tetrahedron*, 1991, **47**, 2801; (f) K. Kondo, M. Seki, T. Kuroda, T. Yamanaka, and T. Iwasaki, *J. Org. Chem.*, 1997, **62**, 2877.

5. (a) L. M. Fuentes, I. Shinkai, A. King, R. Purick, R. A. Reamer, S. M. Schmitt, L. Cama, and B. G. Christensen, *J. Org. Chem.*, 1987, **52**, 2563; (b) M. Kitamura, K. Nagai, Y. Hsiao, and R. Noyori, *Tetrahedron Lett.*, 1990, **31**, 549.
6. T. Iimori, Y. Ishida, and M. Shibasaki, *Tetrahedron Lett.*, 1986, **27**, 2153.
7. M. K. Gurjar, M. N. Bhanu, V. B. Khare, A. Bhandari, M. N. Deshmukh, and A. V. Rama Rao, *Tetrahedron*, 1991, **47**, 7117.
8. J. S. Prasad and L. S. Liebeskind, *Tetrahedron Lett.*, 1987, **28**, 1857.
9. (a) T. Murayama, A. Yoshida, T. Kobayashi, and T. Miura, *Tetrahedron Lett.*, 1994, **35**, 2271; (b) W.-B. Choi, H. R. O. Churchill, J. E. Lynch, A. S. Thompson, G. R. Humphrey, R. P. Volante, P. J. Reider, and I. Shinkai, *Tetrahedron Lett.*, 1994, **35**, 2275.
10. K. Nozaki, W. Li, T. Horiuchi, H. Takaya, T. Saito, A. Yoshida, K. Matsumura, Y. Kato, T. Imai, T. Miura, and H. Kumobayashi, *J. Org. Chem.*, 1996, **61**, 7658.
11. M. Anada, N. Watanabe, and S. Hashimoto, *Chem. Commun.*, 1998, 1517.
12. P. Brown and R. Southgate, *Tetrahedron Lett.*, 1986, **27**, 247.
13. For a review on double asymmetric synthesis, see: S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.
14. For related works, see: (a) S. Hashimoto, N. Watanabe, K. Kawano, and S. Ikegami, *Synth. Commun.*, 1994, **24**, 3277; (b) M. P. Doyle and A. V. Kalinin, *Tetrahedron Lett.*, 1996, **37**, 1371; (c) M. P. Doyle, A. V. Kalinin, and D. G. Ene, *J. Am. Chem. Soc.*, 1996, **118**, 8837.
15. As might be expected, the stereochemical outcome of cyclization of α-diazoacetoacetamide (**11**) was found to be heavily dependent on the chirality of the substrate rather than on that of the catalyst. The ratio of **6**:**12** as a function of the dirhodium(II) catalyst is as follows: $Rh_2(OAc)_4$, 14:86; Rh_2(*R*-PTPA)$_4$, 13:87; Rh_2(*S*-PTPA)$_4$, 40:60.
16. D. H. Shih, J. A. Fayter, L. D. Cama, B. G. Christensen, and J. Hirshfield, *Tetrahedron Lett.*, 1985, **26**, 583.
17. M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri, and M. M. Pearson, *J. Am. Chem. Soc.*, 1993, **115**, 958.
18 D. F. Taber, K. K. You, and A. L. Rheingold, *J. Am. Chem. Soc.*, 1996, **118**, 547.
19. M. P. Doyle, M. S. Shanklin, S.-M. Oon, H. Q. Pho, F. R. van der Heide, and W. R. Veal, *J. Org. Chem.*, 1988, **53**, 3384.
20. M. Anada, T. Sugimoto, N. Watanabe, M. Nakajima, and S. Hashimoto, *Heterocycles*, 1999, **50**, 969.
21. S. Hashimoto, N. Watanabe, T. Sato, M. Shiro, and S. Ikegami, *Tetrahedron Lett.*, 1993, **34**, 5109.
22. S. Hashimoto, N. Watanabe, M. Anada, and S. Ikegami *J. Synth. Org. Chem. Jpn.*, 1996, **54**, 988.
23. H. M. L. Davies, W. R. Cantrell, Jr., K. R. Romines, and J. S. Baum, *Org. Synth.*, 1992, **70**, 93.
24. K. Balenović and N. Bregant, *Croat. Chem. Acta*, 1960, **32**, 57.
25. S. Hashimoto, N. Watanabe, and S. Ikegami, *Tetrahedron. Lett.*, 1990, **31**, 5173.

Received, 13th May, 1999